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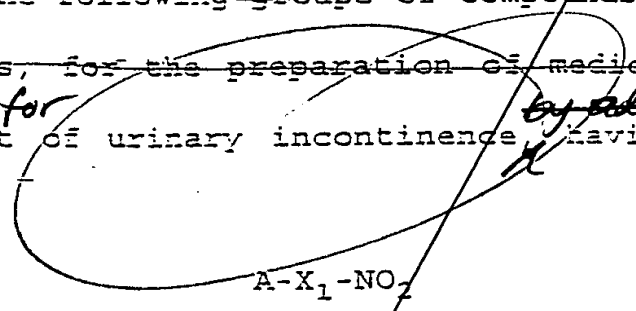
CLAIMS

~~Use of the following groups of compounds, or their compositions, for the preparation of medicaments for the~~ A method for treatment of urinary incontinence ~~by~~ by administering compounds having the ~~general~~ formula:



$A\text{-}X_1\text{-}NO_2$

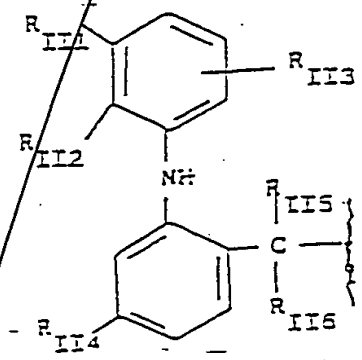
or their salts, where:

A = $R(COX)_t$ where t is an integer 0 or 1;

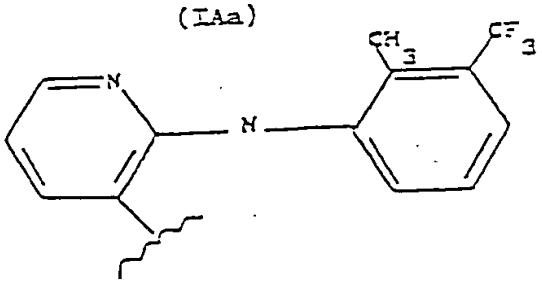
X = O, NH, NR_{1C} where R_{1C} is a linear or branched alkyl having from 1 to 10 C atoms;

R is chosen from the following groups:

* Group I A), where t = 1,



(IAa)



(IAb)

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where:

R_{II5} is H, a linear or whenever possible branched C_1-C_3 alkyl;

R_{II6} has the same meanings as R_{II5}, or when R_{II5} is H it can be benzyl;

R_{II1}, R_{II2} and R_{II3} are equal or different one from the other and are hydrogen, linear or whenever possible branched C_1-C_6 alkyl or C_1-C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{II1} or bromine;

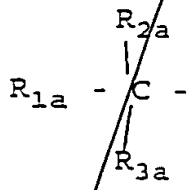
preferred are the compounds where R_{II1}, R_{II2} and R_{II4} are H, and R_{II3} is Cl and R_{II3} is in the ortho position to NH; R_{II5} and R_{II6} are H, X is equal to O, and X_1 is $(CH_2-CH_2-O)_2$;

(I Ab) is the residue of 2-[[2-methyl-3-(trifluoromethyl)phenyl]amino]-3-pyridinecarboxylic acid and when -COOH is present it is known as flunixin.

The compounds preferred are those where X = O;

* II A) chosen from the following:

where, when t = 1, R is



where R_{2a} and R_{3a} are H, a linear or whenever possible

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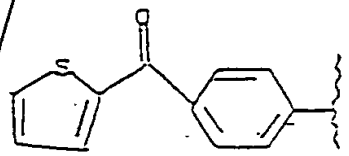
branched substituted or non-substituted C_1-C_{12} alkyl, allyl, with the proviso that when one of the two is allyl the other is H; preferably R_{2a} is H, alkyl has from 1 to 4 C atoms, R_{3a} is H;

R_{1a} is chosen from

II Aa)



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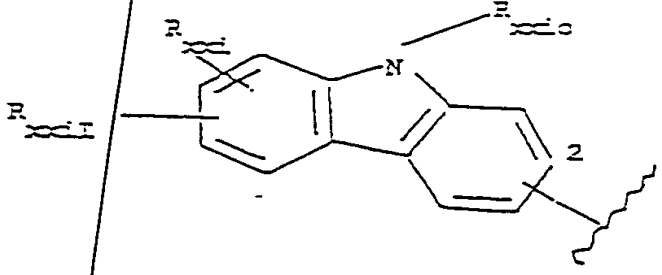
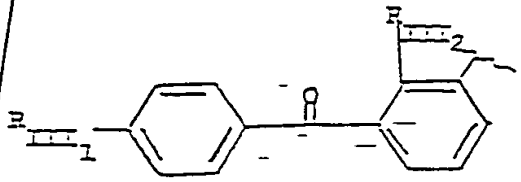


(XXI)



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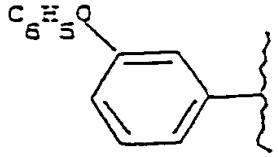

(VII)

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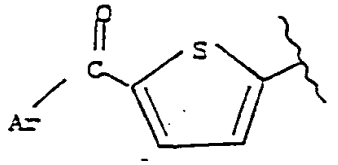
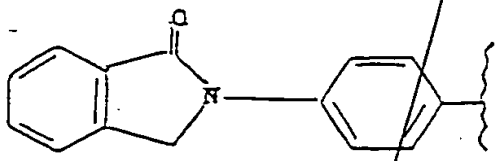


(XXXV)



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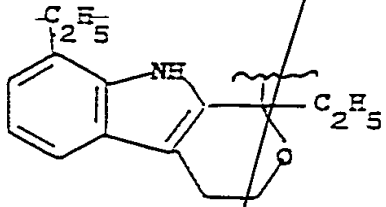

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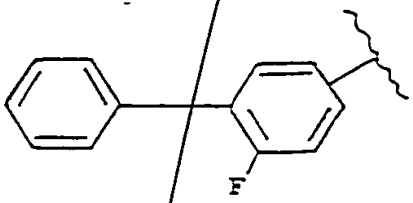

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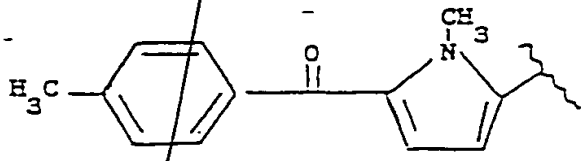

(X)

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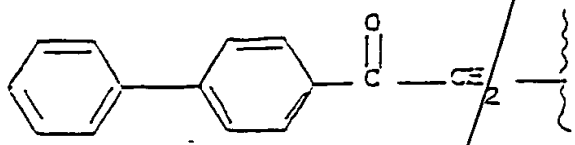


(III)

where meanings are as follows:

- in the compounds of formula (IV), residue of ketoprofen:

R_{III1} is H, SR_{III3} where R_{III3} contains from 1 to 4 C linear or whenever possible branched C atoms;

R_{III2} is H, hydroxy;

preferred are the compounds where R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;

- in the compounds of formula (XXI), residue of carprofen:

R_{xxio} is H, a linear or whenever possible branched alkyl having from 1 to 6 carbon atoms, a C_1-C_6 alkoxycarbonyl bound to a C_1-C_6 alkyl, a C_1-C_6 carboxyalkyl, a C_1-C_6 alkanoyl, optionally substituted with halogen, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xxi} is H, halogen, hydroxy, CN, a C_1-C_6 alkyl optionally containing OH groups, a C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} where R_{xxi2} is a C_1-C_6 alkyl; a perfluoroalkyl having from 1-3 C atoms, a C_1-C_6 carboxyalkyl optio-

nally containing OH groups, NO_2, sulphamoyl, dialkyl sulphamoyl with the alkyl having from 1 to 6 C atoms, or difluoroalkylsulphonyl with the alkyl having from 1 to 3 C atoms;

R_{xxi1} is halogen, CN, a C_1-C_6 alkyl containing one or more OH groups, a C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy,

SR_{III3} is as above defined, a perfluoroalkyl having from 1 to 3 C atoms, hydroxy, a carboxyalkyl having from 1 to 6 C atoms, NO_2, amino, a mono- or dialkylamino having from 1 to 6 C atoms, sulphamoyl, a dialkyl sulphamoyl having from 1 to 6 C atoms, or difluoroalkylsulphamoyl as above defined; or R_{xxi} jointly with R_{xxi1} is an alkylene dioxy having from 1 to 6 C atoms;

preferred are the compounds where R_{xxio} is H, the connecting bridge is at position 2, R_{xxi} is H, R_{xxi1} is chlorine and is in the para position to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;

- in the compounds of formula (XXXV), residue of thiaprofenic acid: Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, an alkanoyl or alkoxy having from 1 to 6 C atoms, a trialalkyl having from 1-6 C atoms, preferably from 1-3 C atoms, cyclo-

pentyl o-hexyl o-heptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

the preferred compounds of formula (XXXV) are those where Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O;

- in the compounds of formula (II), residue of suprofen,

the preferred, where R_{3a} = H, R_{2a} = CH_3 and X = O;

- in the compounds of formula (VI),

of which the preferred, indoprofen, when R_{2a} is CH_3 or indobufen, when R_{2a} is equal to H and R_{3a} = CH_3 and X = O;

- in the compounds of formula (VIII),

of which the preferred, etodolac, when R_{3a} = R_{2a} = H and X = O;

- in the compounds of formula (VII),

of which the preferred, fenoprofen, when R_{3a} = H, R_{2a} = CH_3 and X = O;

- in the compounds of formula (III),

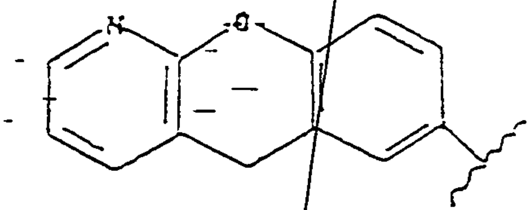
of which the preferred, fenbufen, when R_{3a} = R_{2a} = H and X = O;

- in the compounds of formula (X), residue of tolmetin, when R_{3a} = R_{2a} = H and X = O;

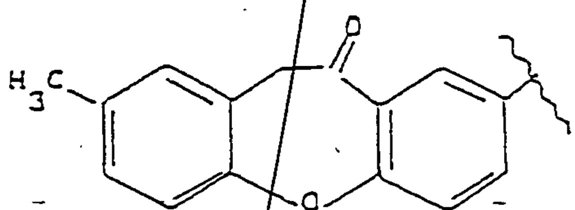
- in the compounds of formula (IX), residue of flurbi-

profen, when $R_{3a} = H$, $R_{2a} = CH_3$ and $X = O$;

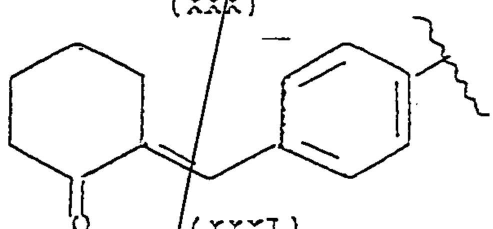
II Ab):



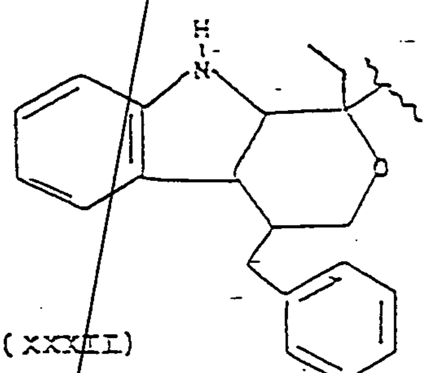
IIIa)



(XXX)



(XXXI)



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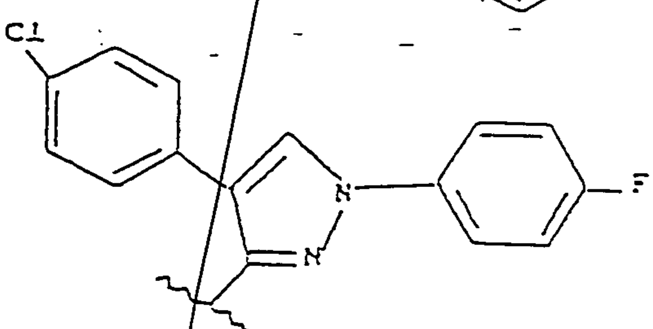

(XXXIII)

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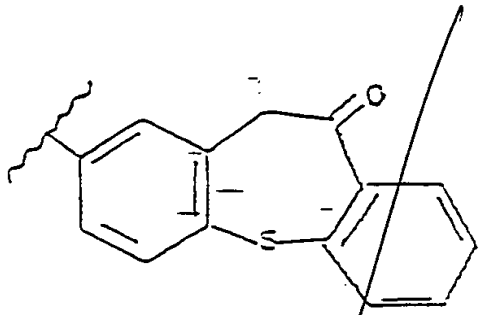
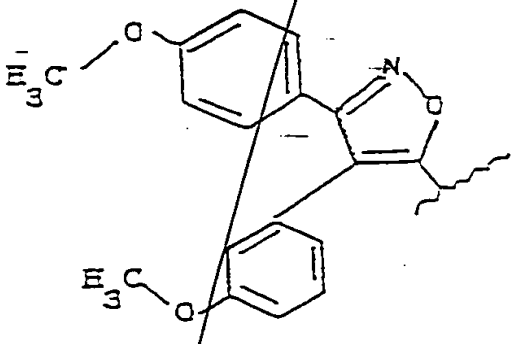


(XXXVI)



(XXXVII)

where the meanings are as follows:

- when IIIa) contains $-CH(CH_3)-COOH$ it is known as pranoprofen: α-methyl-5H-[1] benzopyran [2,3-b]pyridine-7-acetic acid; preferred R_{2a} = H, R_{3a} = CH_3 and X = O;

- when residue (XXX) contains $-CH(CH_3)-COOH$ it is known as bermoprofen: dibenz [b,f] oxepin-2-acetic acid, preferred is X = O, R_{2a} = H, R_{3a} = CH_3;

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- residue (XXXI) is known as CS-670: 2-[4-(2-oxo-1-cyclohexylidenemethyl)phenyl]propionic acid, when the radical is $-CH(CH_3)-COOH$; preferred R_{2a} = H, R_{3a} = CH_3 and X = O;

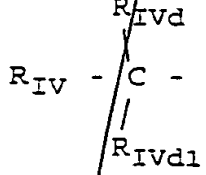
- residue (XXXII) derives from the known pemedolac which contains group $-CH_2COOH$, preferred R_{2a} = R_{3a} = H and X = O;

- when residue (XXXIII) is saturated with $-CH_2COOH$ it is known as pyrazolac: 4-(4-chlorophenyl)-1-(4-fluorophenyl)3-pyrazolyl acid derivatives; preferred R_{2a} = R_{3a} = H and X = O;

- when residue (XXXVI) is saturated with $-CH(CH_3)-COO-$ it is known as zaltoprofen. When the residue is saturated with a hydroxy or amine group or the acid salts, the compounds are known as dibenzothiepin-derivatives. Preferred R_{2a} = H, R_{3a} = CH_3 and X = O;

- when residue (XXXVII) is CH_2-COOH it derives from the known mofezolac: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid; preferred are R_{2a} = R_{3a} = H, t = 1, X = O.

* Group IIIA), where t = 1,



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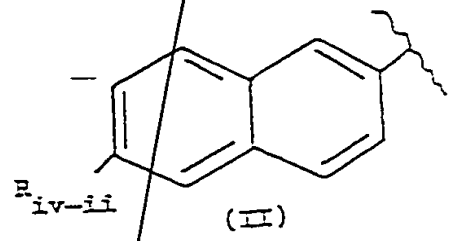
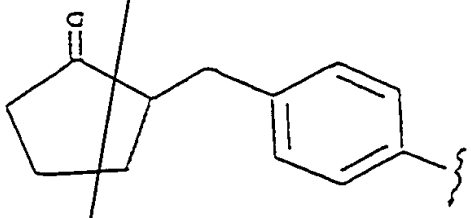
where:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or whenever possible branched C_1-C_6 alkyl, preferably C_1 and C_2, or difluoroalkyl with the alkyl having from 1 to 6 C atoms, preferred is C_1, or R_{IVd} and R_{IVd1} jointly form a methylene group;

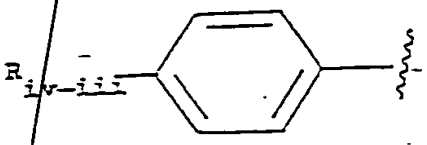
R_{IV} has the following meaning:



(II)



(X)



(III)

where the compounds of group IIIA) have the following meanings:

- in the compounds of formula (II):

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R_{IV-II} is an alkyl having from 1 to 6 C atoms, a cycloalkyl having from 3 to 7 C atoms, an alcoxymethyl having from 1 to 7 C atoms, a trifluoroalkyl having from 1 to 3 C atoms, vinyl, ethynyl, halogen, an alkoxy having from 1 to 6 C atoms, a difluoroalkoxy with the alkyl having from 1 to 7 C atoms, an alkoxymethyloxy having from 1 to 7 C atoms, an alkylthiomethyloxy with the alkyl having from 1 to 7 C atoms, an alkylmethylthio with the alkyl having from 1 to 7 C atoms, cyano, difluoromethylthio, a substituted phenyl- or phenylalkyl with the alkyl having from 1 to 8 C atoms; preferably R_{IV-II} is CH_3O, R_{IVd} is H and R_{IVd1} is CH_3, and is known as the residue of naproxen;

X = NH and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$; also preferred is the same compound where X is equal to O;

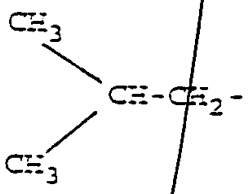
- in the preferred compounds of formula (X), for which the residue of loxoprofen has been shown, R_{IVd} is H and R_{IVd1} is CH_3, X = NH or O and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$;

- in the compounds of formula (III):

R_{IV-III} is a C_2-C_5 alkyl, even branched when possible, a C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, a cycloalkyl having from 5 to 7 C atoms, optionally sub-

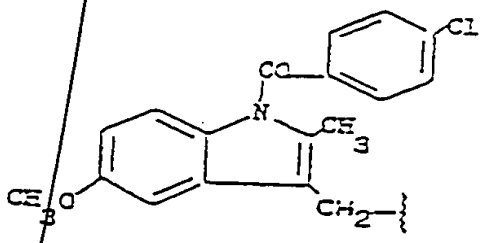
stituted at position 1 by a C_1-C_2 alkyl;

preferred is the compound where R_{IV-III} is



and R_{IVd} = H, R_{IVd1} is CH_3, a compound known as the residue of ibuprofen; X = NH and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$; also preferred is the same compound where X = O;

* Group IV A)



(IV)

where A = RCOO, t = 1,

of which the residue of the known indomethacin has been shown.

* Group V A) chosen from the following:

- V Aa) fenamates chosen from the following,

where t = 1

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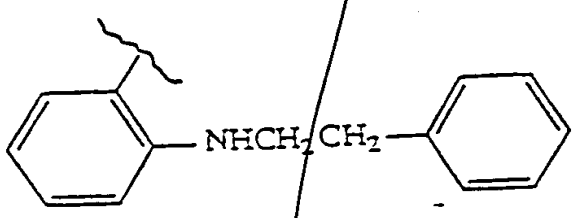
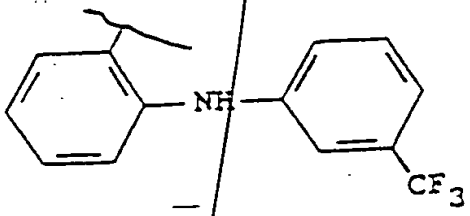
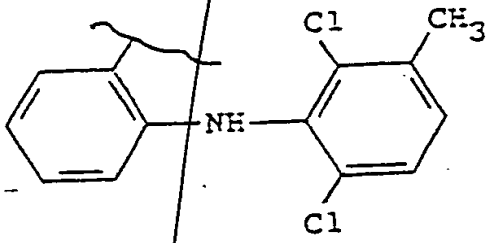


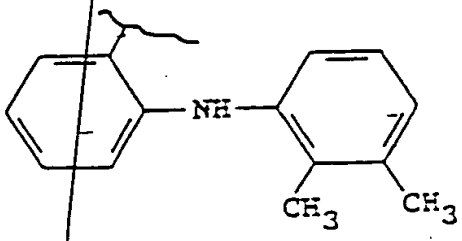
(V Aa1)



(V Aa2)



(V Aa3)



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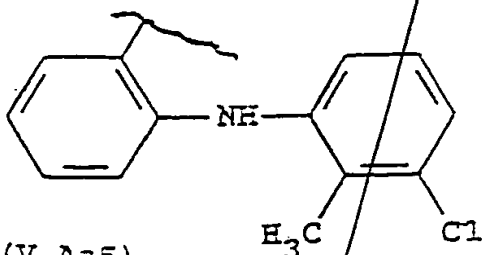
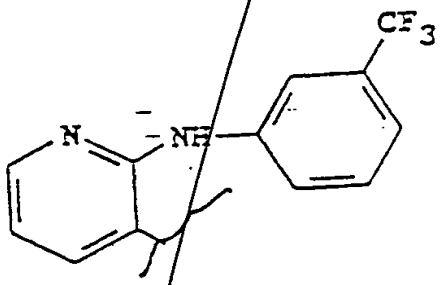


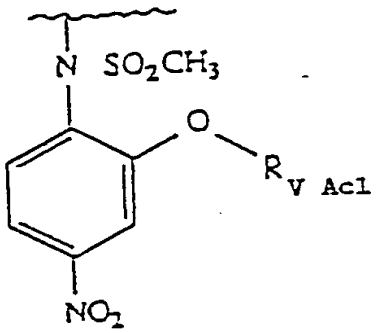
(V Aa5)

- V Ab), derivatives of niflumic acid, where t = 1:

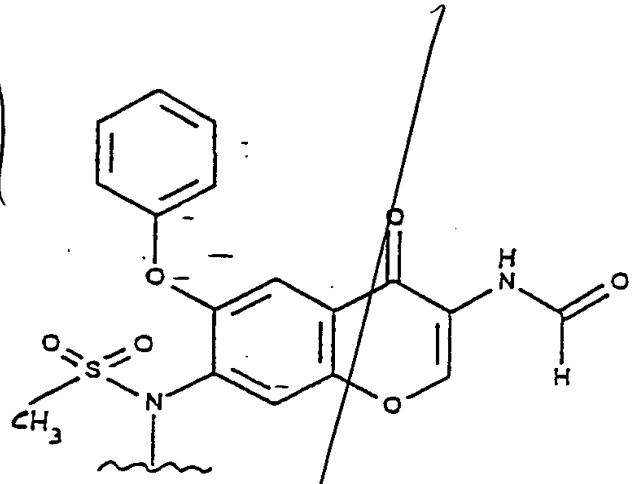


(V Ab1)

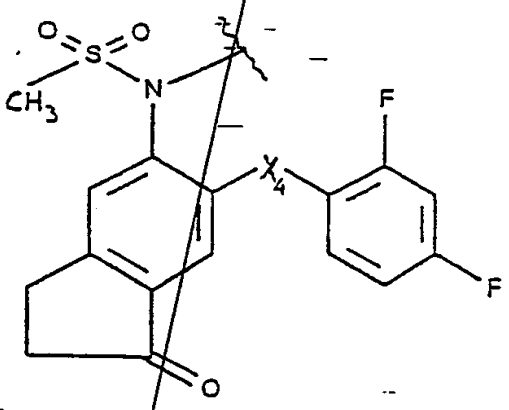
- V Ac), COX_2 inhibitors, where t = 0 and R is as follows:



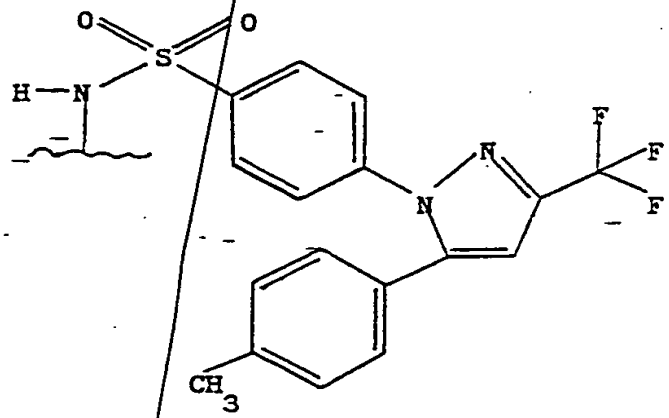
(V Ac1)



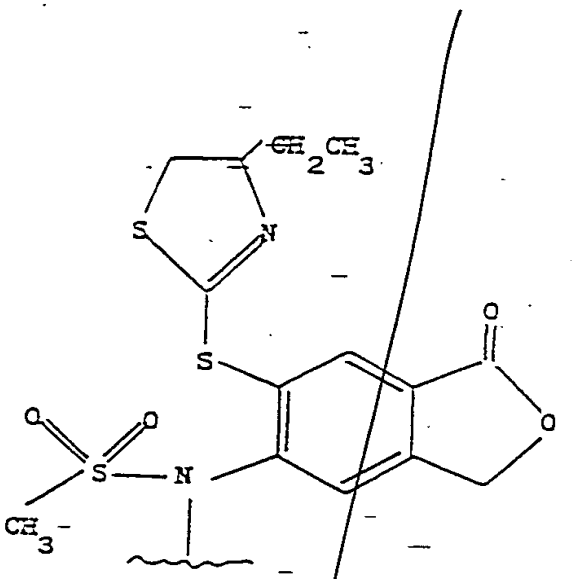
(V Ac2)



(V Ac3)

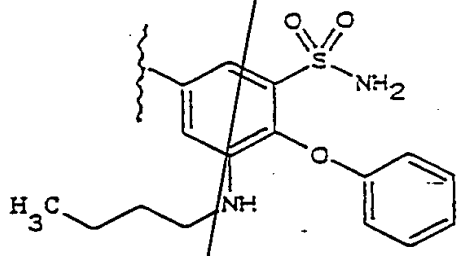


(V Ac4)

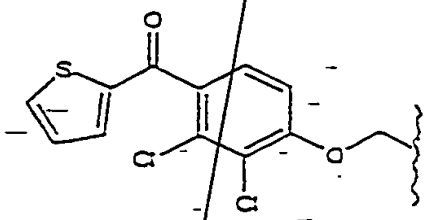


(V Ac5)

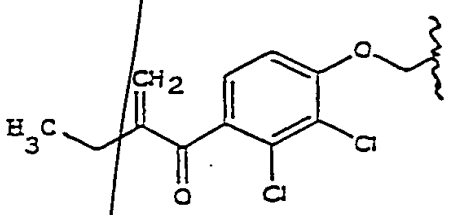
- V Ad) derivatives of diuretics when t = 1 and R is as follows:



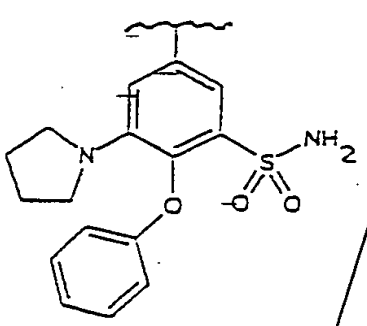
(V Ad1)



(V Ad2)

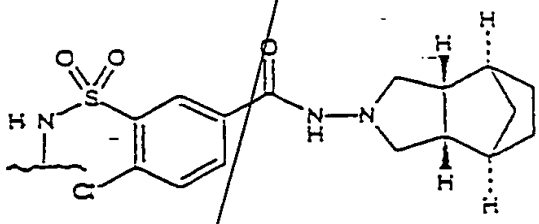


(V Ad3)

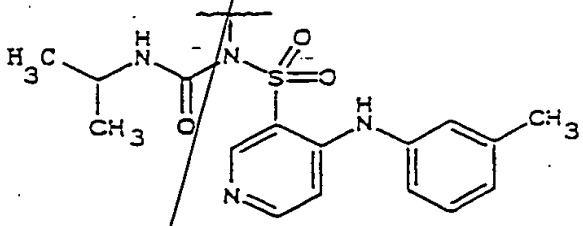


(V Ad4)

- V Ae) derivatives of diuretics when t = 0 and R is as follows:

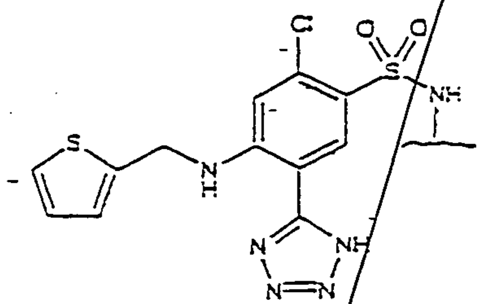


(V Ae1)

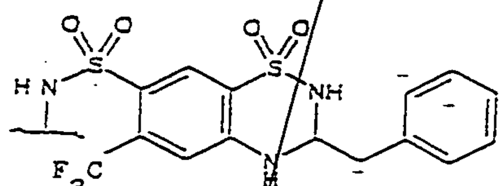


(V Ae2)

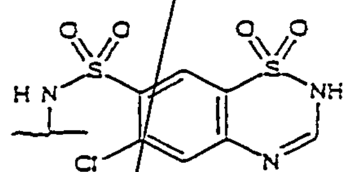
Sub D' cont



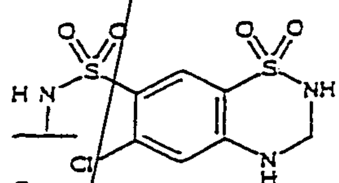
(V Ae3)



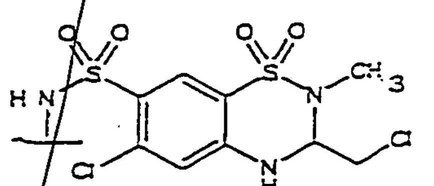
(V Ae4)



(V Ae5)



(V Ae6)



(V Ae7)

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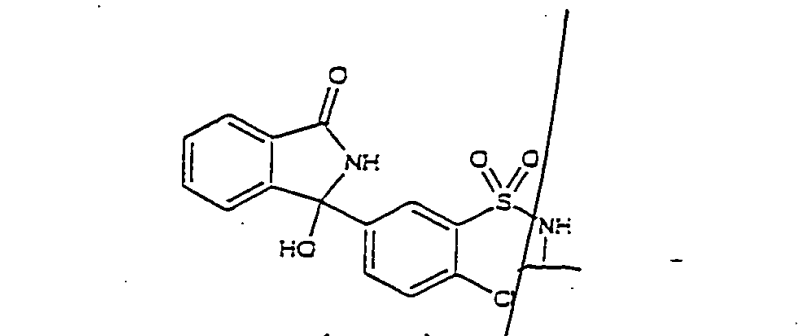
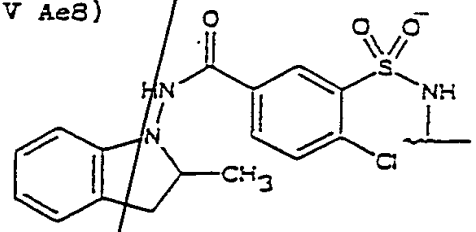
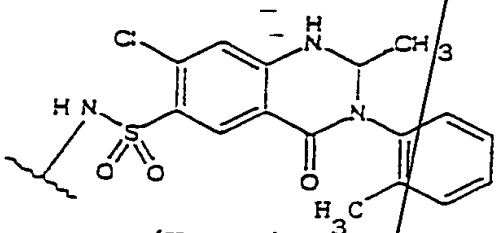
Sub D' cont



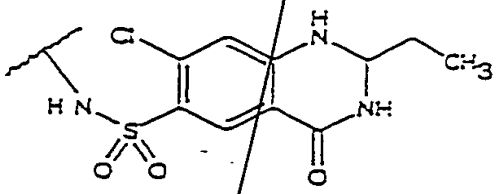
(V Ae8)



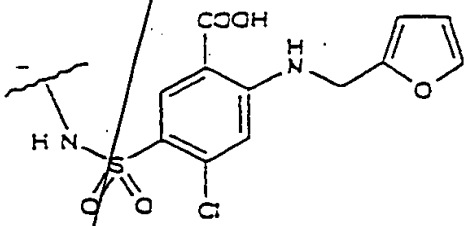
(V Ae9)



(V Ae10)



(V Ae11)



(V Ae12)

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where the meaning in group V A) is as follows:

- in compounds (V Aa1) the residue of enfenamic acid, 2-[(2-phenylethyl)amino]benzoic acid, has been shown;
- in compounds (V Aa2) the residue of flufenamic acid, 2-[[3-(trifluoromethyl)phenyl]-amino]benzoic acid, has been shown;
- in compounds (V Aa3) the residue of meclofenamic acid, 2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid, has been shown;
- in compounds (V Aa4) the residue of mefanamic acid, 2-[(2,3-dimethylphenyl)amino]benzoic acid, has been shown;
- in compounds (V Aa5) the residue of tolfenamic acid, 2-[(3-chloro-2-methylphenyl)amino]benzoic acid, has been shown;
- in compounds (V Ab1) the residue of niflumic acid, 2-[[3-(trifluoromethyl)phenyl]amino]-3-pyridine carboxylic acid, has been shown;
- in compounds (V Ac1) $_{R_{vac1}}$ attached to the oxygen atom in position 2 of the benzene ring of N-(4-nitrophenyl)methansulphonamide can be phenyl or cycloexane. When R_{vac1} is phenyl the residue is that of nimesulide;
- in compounds (V Ac2) the residue of 3-formylamino-7-

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methylsulfonylamino-6-phenoxy-4H-1-bezopyran-4-one has been shown;

- in compounds (V Ac3) the atom X_4 that links the radical 2,4-difluorothiophenyl to position 6 of the indanone ring of the residue 5-methanesulfonamido-1-indanone can be sulfur or oxygen;

- in compounds (V Ac4) the residue of celecoxib 4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl] benzensulphonamide, has been shown;

- in compounds (V Ac5) the residue of 6-[2-(3-ethyl-2,3-dihydro-thiazolyl)thio-5-methanesulphonamido-3H-isobenzonfuran-1-one has been shown.

- in compounds (V Ad1) the residue of bumetanide 3-(Aminosulfonyl)-5-(butylamino)-4-phenoxybenzoic acid has been shown;

- in compounds (V Ad2) the residue of ticrynafen [2,3-Dichloro-4-(2-thienylcarbonyl)-phenoxy]acetic acid has been shown;

- in compounds (V Ad3) the residue of ethacrynic acid [2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxy]acetic acid, has been shown;

- in compounds (V Ad4) the residue of piretanide 3-(Aminosulfonyl)-4-phenoxy-5-(1-pyrrolidinyl)benzoic

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acid has been shown.

- in compounds (V Ae1) the residue of tripamide (3aα, 4α, 7α, 7aα)-3-(Aminosulphonyl)-4-chloro-N-(octaidro-4,7-metano-2H-isoindol-2-yl)benzamide has been shown.

- in compounds (V Ae2) the residue of torsemide N-[[(1-Methylethyl)amino]carbonyl]4-[(3-methylphenyl)amino]-3-pyrinesulfonamide has been shown;

-in compounds (V Ae3) the residue of azosemide 2-Chloro-5-(1H-tetrazol-5-yl)-4-[(2-thienylmethyl)amino]benzensulphonamide has been shown;

- in compounds (V Ae4) the residue of bendroflumethiazide 3,4-Dihydro-3-(phenyl-methyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;

- in compounds (V Ae5) the residue of chlorothiazide 6-Chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;

- in compounds (V Ae6) the residue of hydrochlorotiazide 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;

- in compounds (V Ae7) the residue of methylclothiazide (6-Chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has

been shown;

- in compounds (V Ae8) the residue of chlorthalidone 2-Chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)benzensulfonamide has been shown;

- in compounds (V Ae9) the residue of Indapamide 3-(Aminosulfonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl)benzamide has been shown;

- in compounds (VAe10) the residue of metolazone 7-Chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazolinesulfonamide has been shown;

- in compounds (V Ae11) the residue of quinetazone 7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-quinazoline-sulfonamide has been shown;

- in compounds (V Ae12) the residue of furosemide 5-(Aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid has been shown.

X_1 in formula $A\text{-}X_1\text{-}NO_2$ is a bivalent connecting bridge chosen from the following:

- YO

where Y is a linear or whenever possible branched C_1-C_{20} alkylene, preferably having from 2 to 5 carbon atoms, or an optionally substituted cycloalkylene having from 5 to 7 carbon atoms;

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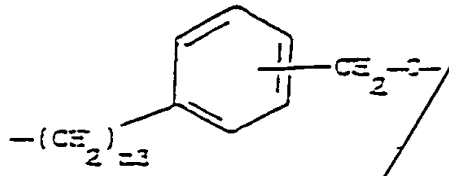
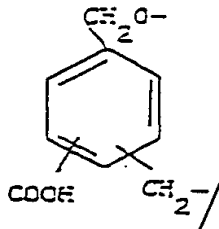
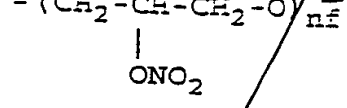
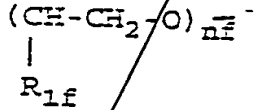


where n_3 is an integer from 0 to 3;





where nf' is an integer from 1 to 6, preferably from 2 to 4;



where R_{1f} = H, CH_3 and nf is an integer from 1 to 6, preferably from 2 to 4.

2. ~~Use of the compounds~~ the method according to Claim 1, in which R is chosen from groups IV A) and V A).

3. Compounds or their compositions for use as medicaments from group V A) in Claim 1.

4. Compounds from group V A) according to Claim 1.

5. Compounds or their compositions for use as medicaments

from group V A) according to Claim 3 for the treatment of musculoskeletal disease of an inflammatory nature, respiratory disease of an inflammatory nature, gynaecological and obstetrical disease including early delivery, pre-eclampsia and dysmenorrhoea, cardiovascular disease including re-stenosis, gastrointestinal tumours.

6. Use of the following compounds, or their compositions, for the preparation of medicaments for the following therapeutical applications:

treatment of respiratory disease: bronchitis, in particular asthma: groups from I A) to V A) in Claim 1;

gynaecological and obstetrical disease including early delivery, pre-eclampsia and dysmenorrhoea: groups from I A) to V A) in Claim 1 and group VI A) as defined below;

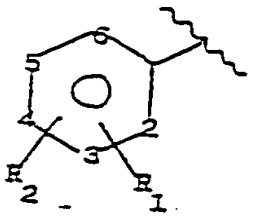
vascular disease including re-stenosis: groups from I A) to V A) in Claim 1 and group VI A);

gastrointestinal tumours: groups from I A) to V A) in Claim 1 and group VI A);

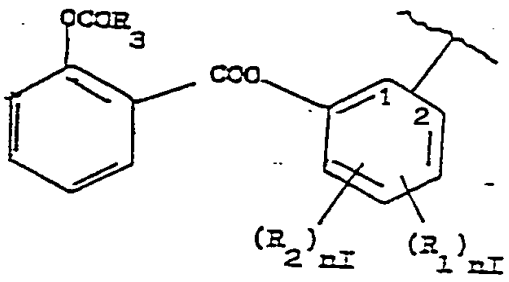
the compounds in group VI A) have the general formula

$$A\text{-}X_1\text{-}NO_2,$$

of Claim 1, where t = 1, include the following:



(Ia)



(Ib)

where:

R_1 is group $OCOR_3$; where R_3 is methyl, ethyl or a linear or branched C_3-C_5 alkyl, or the residue of a single-ring heterocycle having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently chosen from O, N and S;

R_2 is hydrogen, hydroxy, halogen, a linear or whenever possible branched alkyl having from 1 to 4 C atoms, a linear or whenever possible branched alcoxyl having from 1 to 4 C atoms; a linear or whenever possible branched perfluoroalkyl having from 1 to 4 C atoms, for example trifluoromethyl, nitro, amino, mono- or

di(C_{1-4})alkylamino;

R_1 and R_2 jointly are the dioxymethylene group, with the proviso that when X = NH, then X_1 is ethylene and R_2 = H; R_1 cannot be $OCOR_3$ at position 2 when R_3 is methyl; nI being an integer from 0 to 1;

preferably in Ia), X is equal to O or NH, R_1 is acetoxy, preferably at position 3 or 4, most preferably in the ortho position to CO. X_1 is ethylene or $(CH_2CH_2O)_2$, R_2 is hydrogen or halogen, most preferred are the following A X_1 NO_2 compounds: 3-acetoxy-N-(2-nitroxyethyl)-benzamide, 4-acetoxy-N-(2-nitroxyethyl)-benzamide, 3-acetoxy-N-(5-nitroxypenthyl)-benzamide, 2-acetoxy-N-(5-nitroxypenthyl)-benzamide, N-2-(nitroxyethyl)-2-propionoxybenzamide, 2-acetoxy-2-nitroxyethylbenzoate, 2-acetoxy-N-(cis-2-nitroxycyclohexyl)-benzamide, 2-acetoxy-4-chloro-N-(2-nitroxyethyl)-benzamide, N-(2-nitroxyethyl)-2-((4-thiazolindinyl)carbonyloxy)-benzamide hydrochloride, 2-nicotinoyloxy-N-(2-nitroxyethyl)-benzamide, 2-acetoxy-5-nitroxypenthylbenzoate;

preferably in Ib) R_3 = CH_3, nI = 0;

X is equal to O, X_1 is ethylene; in this case Ib) is the residue of acetylsalicylsalicylic acid.

add C1 / 03 / X1